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(54) Title: **FARNESYL PROTEIN TRANSFERASE INHIBITOR COMBINATIONS WITH AN HER2 ANTIBODY**

(57) Abstract: The present invention is concerned with combinations of a farnesyl transferase inhibitor and an HER2 antibody for inhibiting the growth of tumor cells and useful in the treatment of cancer.

WO 01/64246 A2

FARNESYL PROTEIN TRANSFERASE
INHIBITOR COMBINATIONS WITH AN HER2 ANTIBODY

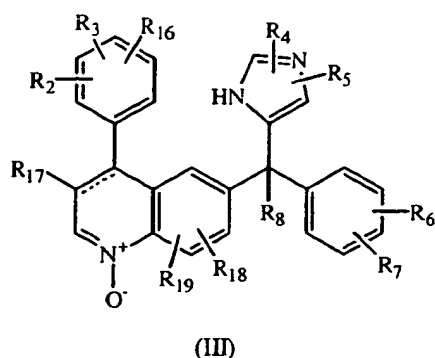
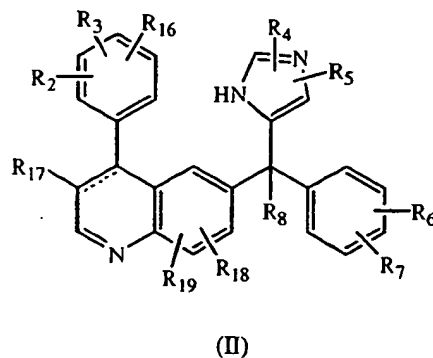
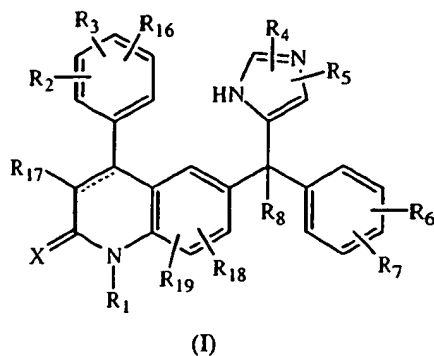
5 The present invention is concerned with combinations of a farnesyl transferase inhibitor and an HER2 antibody for inhibiting the growth of tumor cells. and useful in the treatment of cancer.

10 Oncogenes frequently encode protein components of signal transduction pathways which lead to stimulation of cell growth and mitogenesis. Oncogene expression in cultured cells leads to cellular transformation, characterized by the ability of cells to grow in soft agar and the growth of cells as dense foci lacking the contact inhibition exhibited by non-transformed cells. Mutation and/or overexpression of certain oncogenes is frequently associated with human cancer. A particular group of
15 oncogenes is known as ras which have been identified in mammals, birds, insects, mollusks, plants, fungi and yeasts. The family of mammalian ras oncogenes consists of three major members ("isoforms") : H-ras, K-ras and N-ras oncogenes. These ras oncogenes code for highly related proteins generically known as p21^{ras}. Once attached to plasma membranes, the mutant or oncogenic forms of p21^{ras} will provide a signal
20 for the transformation and uncontrolled growth of malignant tumor cells. To acquire this transforming potential, the precursor of the p21^{ras} oncoprotein must undergo an enzymatically catalyzed farnesylation of the cysteine residue located in a carboxyl-terminal tetrapeptide. Therefore, inhibitors of the enzyme that catalyzes this modification, farnesyl protein transferase, will prevent the membrane attachment of
25 p21^{ras} and block the aberrant growth of ras-transformed tumors. Hence, it is generally accepted in the art that farnesyl transferase inhibitors can be very useful as anticancer agents for tumors in which ras contributes to transformation.

30 Since mutated, oncogenic forms of ras are frequently found in many human cancers, most notably in more than 50 % of colon and pancreatic carcinomas (Kohl et al., Science, vol 260, 1834 - 1837, 1993), it has been suggested that farnesyl transferase inhibitors can be very useful against these types of cancer. Following further investigations, it has been found that a farnesyl transferase inhibitor is capable of demonstrating antiproliferative effects in vitro and antitumor effects in vivo in a variety
35 of human tumor cell lines with and without ras gene mutations.

WO-97/21701 describes the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting (imidazoly-5-yl)methyl-2-quinolinone derivatives of formulas (I), (II) and (III), as well as intermediates of formula (II) and (III) that are metabolized in vivo to the compounds of formula (I). The compounds of formulas (I),

(II) and (III) are represented by



the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein the dotted line represents an optional bond;

X is oxygen or sulfur;

R¹ is hydrogen, C₁₋₁₂alkyl, Ar¹, Ar²C₁₋₆alkyl, quinolinylC₁₋₆alkyl, pyridyl-C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl, aminoC₁₋₆alkyl, or a radical of formula -Alk¹-C(=O)-R⁹, -Alk¹-S(O)-R⁹ or -Alk¹-S(O)₂-R⁹, wherein Alk¹ is C₁₋₆alkanediyl,

R⁹ is hydroxy, C₁₋₆alkyl, C₁₋₆alkyloxy, amino, C₁₋₈alkylamino or C₁₋₈alkylamino substituted with C₁₋₆alkyloxycarbonyl;

R², R³ and R¹⁶ each independently are hydrogen, hydroxy, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, C₁₋₆alkyloxyC₁₋₆alkyloxy, aminoC₁₋₆alkyloxy, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy, Ar¹, Ar²C₁₋₆alkyl, Ar²oxy,

-3-

Ar²C₁₋₆alkyloxy, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C₂₋₆alkenyl, 4,4-dimethyloxazolyl; or

when on adjacent positions R² and R³ taken together may form a bivalent radical of formula

- 5 -O-CH₂-O- (a-1),
 -O-CH₂-CH₂-O- (a-2),
 -O-CH=CH- (a-3),
 -O-CH₂-CH₂- (a-4),
 -O-CH₂-CH₂-CH₂- (a-5), or
 10 -CH=CH-CH=CH- (a-6);

R⁴ and R⁵ each independently are hydrogen, halo, Ar¹, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, amino, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylS(O)C₁₋₆alkyl or C₁₋₆alkylS(O)₂C₁₋₆alkyl;

R⁶ and R⁷ each independently are hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy, Ar²oxy, trihalomethyl, C₁₋₆alkylthio, di(C₁₋₆alkyl)amino, or
 15 when on adjacent positions R⁶ and R⁷ taken together may form a bivalent radical of formula

- O-CH₂-O- (c-1), or
 -CH=CH-CH=CH- (c-2);

20 R⁸ is hydrogen, C₁₋₆alkyl, cyano, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylcarbonylC₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, carboxyC₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)-aminoC₁₋₆alkyl, imidazolyl, haloC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, or a radical of formula

- 25 -O-R¹⁰ (b-1),
 -S-R¹⁰ (b-2),
 -N-R¹¹R¹² (b-3),

wherein R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹, Ar²C₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, or a radical or formula -Alk²-OR¹³
 30 or -Alk²-NR¹⁴R¹⁵;

R¹¹ is hydrogen, C₁₋₁₂alkyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹² is hydrogen, C₁₋₆alkyl, C₁₋₁₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminocarbonyl, Ar¹, Ar²C₁₋₆alkyl, C₁₋₆alkylcarbonyl-C₁₋₆alkyl, a natural amino acid, Ar¹carbonyl, Ar²C₁₋₆alkylcarbonyl, aminocarbonylcarbonyl, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, hydroxy, C₁₋₆alkyloxy, aminocarbonyl, di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl,
 35

amino, C₁-6alkylamino, C₁-6alkylcarbonylamino, or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;

wherein Alk^2 is C_{1-6} alkanediyl;

R¹³ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, hydroxy-

5

C₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;

R^{14} is hydrogen, C₁-6alkyl, Ar¹ or Ar²C₁-6alkyl;

R¹⁵ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹⁷ is hydrogen, halo, cyano, C₁-6alkyl, C₁-6alkyloxycarbonyl, Ar¹;

10 R¹⁸ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or halo;

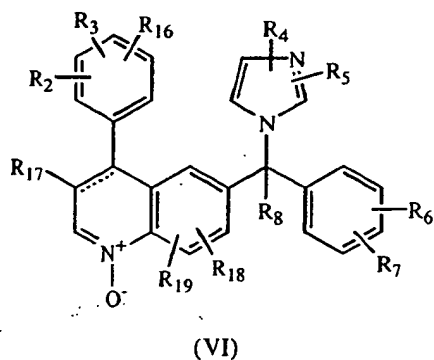
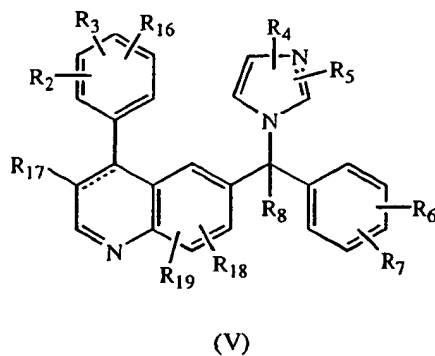
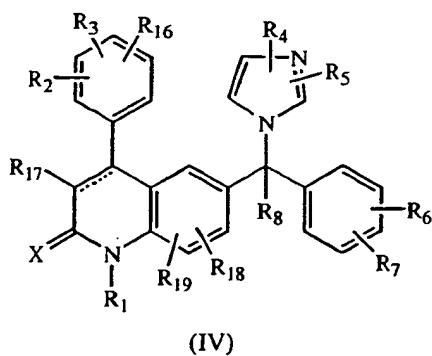
R¹⁹ is hydrogen or C₁₋₆alkyl;

Ar¹ is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo; and

Ar² is phenyl or phenyl substituted with C₁-6alkyl, hydroxy, amino, C₁-6alkyloxy or halo.

15

WO-97/16443 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (IV), as well as intermediates of formula (V) and (VI) that are metabolized in vivo to the compounds of formula (IV). The compounds of formulas (IV), (V) and (VI) are represented by



the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

5 R^1 is hydrogen, C_{1-12} alkyl, Ar^1 , Ar^2C_{1-6} alkyl, quinolinyl C_{1-6} alkyl, pyridyl- C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)-amino C_{1-6} alkyl, amino C_{1-6} alkyl,
or a radical of formula $-Alk^1-C(=O)-R^9$, $-Alk^1-S(O)-R^9$ or $-Alk^1-S(O)_2-R^9$,
wherein Alk^1 is C_{1-6} alkanediyl,

10 R^9 is hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy, amino, C_{1-8} alkylamino or C_{1-8} alkylamino substituted with C_{1-6} alkyloxycarbonyl;

R^2 and R^3 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyloxy, amino- C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, Ar^1 , Ar^2C_{1-6} alkyl,
15 Ar^2oxy , Ar^2C_{1-6} alkyloxy, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6} alkenyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

20 $-O-CH_2-O-$ (a-1),
 $-O-CH_2-CH_2-O-$ (a-2),
 $-O-CH=CH-$ (a-3),
 $-O-CH_2-CH_2-$ (a-4),
 $-O-CH_2-CH_2-CH_2-$ (a-5), or
 $-CH=CH-CH=CH-$ (a-6);

25 R^4 and R^5 each independently are hydrogen, Ar^1 , C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl $S(O)C_{1-6}$ alkyl or C_{1-6} alkyl $S(O)_2C_{1-6}$ alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy or Ar^2oxy ;

30 R^8 is hydrogen, C_{1-6} alkyl, cyano, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl-carbonyl C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, hydroxy-carbonyl C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)-amino C_{1-6} alkyl, halo C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, aminocarbonyl C_{1-6} alkyl, Ar^1 , Ar^2C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkylthio C_{1-6} alkyl;

35 R^{10} is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy or halo;

R^{11} is hydrogen or C_{1-6} alkyl;

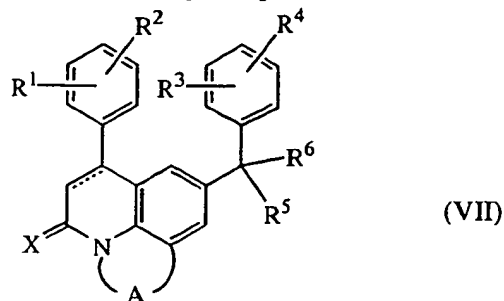
-6-

Ar¹ is phenyl or phenyl substituted with C₁-6alkyl, hydroxy, amino, C₁-6alkyloxy or halo;

Ar² is phenyl or phenyl substituted with C₁-6alkyl, hydroxy, amino, C₁-6alkyloxy or halo.

5

WO-98/40383 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (VII)



10 the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

-A- is a bivalent radical of formula

- | | | | | |
|----|--|--------|---------------------------------------|-----------|
| 15 | -CH=CH- | (a-1), | -CH ₂ -S- | (a-6), |
| | -CH ₂ -CH ₂ - | (a-2), | -CH ₂ -CH ₂ -S- | (a-7), |
| | -CH ₂ -CH ₂ -CH ₂ - | (a-3), | -CH=N- | (a-8), |
| | -CH ₂ -O- | (a-4), | -N=N- | (a-9), or |
| | -CH ₂ -CH ₂ -O- | (a-5), | -CO-NH- | (a-10); |

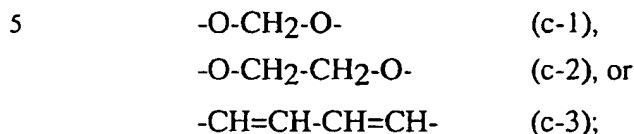
20 wherein optionally one hydrogen atom may be replaced by C₁-4alkyl or Ar¹;

R¹ and R² each independently are hydrogen, hydroxy, halo, cyano, C₁-6alkyl, trihalomethyl, trihalomethoxy, C₂-6alkenyl, C₁-6alkyloxy, hydroxyC₁-6alkyloxy, C₁-6alkyloxyC₁-6alkyloxy, C₁-6alkyloxycarbonyl, aminoC₁-6alkyloxy, mono- or di(C₁-6alkyl)aminoC₁-6alkyloxy, Ar², Ar²-C₁-6alkyl, Ar²-oxy,

25 Ar²-C₁-6alkyloxy; or when on adjacent positions R¹ and R² taken together may form a bivalent radical of formula

- | | | |
|----|--|-----------|
| | -O-CH ₂ -O- | (b-1), |
| | -O-CH ₂ -CH ₂ -O- | (b-2), |
| | -O-CH=CH- | (b-3), |
| 30 | -O-CH ₂ -CH ₂ - | (b-4), |
| | -O-CH ₂ -CH ₂ -CH ₂ - | (b-5), or |
| | -CH=CH-CH=CH- | (b-6); |

R³ and R⁴ each independently are hydrogen, halo, cyano, C₁-6alkyl, C₁-6alkyloxy, Ar³-oxy, C₁-6alkylthio, di(C₁-6alkyl)amino, trihalomethyl, trihalomethoxy, or when on adjacent positions R³ and R⁴ taken together may form a bivalent radical of formula



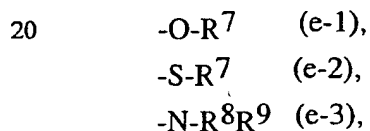
R⁵ is a radical of formula



10 wherein R¹³ is hydrogen, halo, Ar⁴, C₁-6alkyl, hydroxyC₁-6alkyl, C₁-6alkyloxy-C₁-6alkyl, C₁-6alkyloxy, C₁-6alkylthio, amino, C₁-6alkyloxy-carbonyl, C₁-6alkylS(O)C₁-6alkyl or C₁-6alkylS(O)₂C₁-6alkyl;

 R¹⁴ is hydrogen, C₁-6alkyl or di(C₁-4alkyl)aminosulfonyl;

15 R⁶ is hydrogen, hydroxy, halo, C₁-6alkyl, cyano, haloC₁-6alkyl, hydroxyC₁-6alkyl, cyanoC₁-6alkyl, aminoC₁-6alkyl, C₁-6alkyloxyC₁-6alkyl, C₁-6alkylthioC₁-6alkyl, aminocarbonylC₁-6alkyl, C₁-6alkyloxy-carbonylC₁-6alkyl, C₁-6alkylcarbonyl-C₁-6alkyl, C₁-6alkyloxy-carbonyl, mono- or di(C₁-6alkyl)aminoC₁-6alkyl, Ar⁵, Ar⁵-C₁-6alkyloxyC₁-6alkyl; or a radical of formula



 wherein R⁷ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar⁶, Ar⁶-C₁-6alkyl, C₁-6alkyloxy-carbonylC₁-6alkyl, or a radical of formula -Alk-OR¹⁰ or -Alk-NR¹¹R¹²;

25 R⁸ is hydrogen, C₁-6alkyl, Ar⁷ or Ar⁷-C₁-6alkyl;

 R⁹ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, C₁-6alkyloxy-carbonyl, C₁-6alkylaminocarbonyl, Ar⁸, Ar⁸-C₁-6alkyl, C₁-6alkylcarbonyl-C₁-6alkyl, Ar⁸-carbonyl, Ar⁸-C₁-6alkylcarbonyl, aminocarbonyl-carbonyl, C₁-6alkyloxyC₁-6alkylcarbonyl, hydroxy, C₁-6alkyloxy, aminocarbonyl, di(C₁-6alkyl)aminoC₁-6alkylcarbonyl, amino, C₁-6alkylamino, C₁-6alkylcarbonylamino, or a radical or formula -Alk-OR¹⁰ or -Alk-NR¹¹R¹²;

30 wherein Alk is C₁-6alkanediyl;

-8-

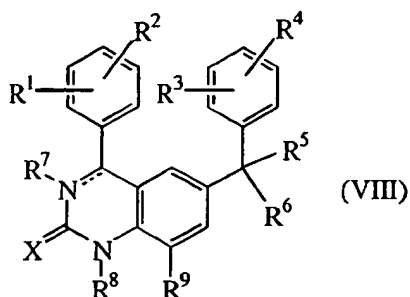
R^{10} is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, hydroxy C_1 -6alkyl, Ar^9 or Ar^9 - C_1 -6alkyl;

R^{11} is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, Ar^{10} or Ar^{10} - C_1 -6alkyl;

5 R^{12} is hydrogen, C_1 -6alkyl, Ar^{11} or Ar^{11} - C_1 -6alkyl; and

Ar^1 to Ar^{11} are each independently selected from phenyl; or phenyl substituted with halo, C_1 -6alkyl, C_1 -6alkyloxy or trifluoromethyl.

10 WO-98/49157 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (VIII)



the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

15 X is oxygen or sulfur;

R^1 and R^2 each independently are hydrogen, hydroxy, halo, cyano, C_1 -6alkyl, trihalomethyl, trihalomethoxy, C_2 -6alkenyl, C_1 -6alkyloxy, hydroxy C_1 -6alkyloxy, C_1 -6alkyloxy C_1 -6alkyloxy, C_1 -6alkyloxycarbonyl, amino C_1 -6alkyloxy, mono- or di(C_1 -6alkyl)amino C_1 -6alkyloxy, Ar^1 , Ar^1 - C_1 -6alkyl, Ar^1 oxy or

20 Ar^1 - C_1 -6alkyloxy;

R^3 and R^4 each independently are hydrogen, halo, cyano, C_1 -6alkyl, C_1 -6alkyloxy, Ar^1 oxy, C_1 -6alkylthio, di(C_1 -6alkyl)amino, trihalomethyl or trihalomethoxy;

R^5 is hydrogen, halo, C_1 -6alkyl, cyano, halo C_1 -6alkyl, hydroxy C_1 -6alkyl, cyano C_1 -6alkyl, amino C_1 -6alkyl, C_1 -6alkyloxy C_1 -6alkyl,

25 C_1 -6alkylthio C_1 -6alkyl, aminocarbonyl C_1 -6alkyl,

C_1 -6alkyloxycarbonyl C_1 -6alkyl, C_1 -6alkylcarbonyl- C_1 -6alkyl,

C_1 -6alkyloxycarbonyl, mono- or di(C_1 -6alkyl)amino C_1 -6alkyl, Ar^1 ,

Ar^1 - C_1 -6alkyloxy C_1 -6alkyl; or a radical of formula

-O- R^{10} (a-1),

30 -S- R^{10} (a-2),

-N- R^{11} R^{12} (a-3),

wherein R^{10} is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, Ar^1 , Ar^1C_1 -6alkyl, C_1 -6alkyloxycarbonyl C_1 -6alkyl, or a radical of formula $-Alk-OR^{13}$ or $-Alk-NR^{14}R^{15}$;

R^{11} is hydrogen, C_1 -6alkyl, Ar^1 or Ar^1C_1 -6alkyl;

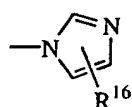
5 R^{12} is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, C_1 -6alkyloxycarbonyl, C_1 -6alkylaminocarbonyl, Ar^1 , Ar^1C_1 -6alkyl, C_1 -6alkylcarbonyl- C_1 -6alkyl, Ar^1 carbonyl, Ar^1C_1 -6alkylcarbonyl, aminocarbonylcarbonyl, C_1 -6alkyloxy C_1 -6alkylcarbonyl, hydroxy, C_1 -6alkyloxy, aminocarbonyl, di(C_1 -6alkyl)amino C_1 -6alkylcarbonyl, amino, C_1 -6alkylamino, C_1 -6alkylcarbonylamino,
10 or a radical of formula $-Alk-OR^{13}$ or $-Alk-NR^{14}R^{15}$;
 wherein Alk is C_1 -6alkanediyl;

R^{13} is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, hydroxy- C_1 -6alkyl, Ar^1 or Ar^1C_1 -6alkyl;

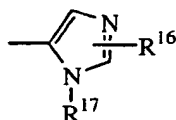
15 R^{14} is hydrogen, C_1 -6alkyl, Ar^1 or Ar^1C_1 -6alkyl;

R^{15} is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, Ar^1 or Ar^1C_1 -6alkyl;

R^6 is a radical of formula



(b-1),



(b-2),

20 wherein R^{16} is hydrogen, halo, Ar^1 , C_1 -6alkyl, hydroxy C_1 -6alkyl, C_1 -6alkyloxy- C_1 -6alkyl, C_1 -6alkyloxy, C_1 -6alkylthio, amino, C_1 -6alkyloxycarbonyl, C_1 -6alkylthio C_1 -6alkyl, C_1 -6alkylS(O) C_1 -6alkyl or C_1 -6alkylS(O) $_2$ C_1 -6alkyl;

R^{17} is hydrogen, C_1 -6alkyl or di(C_1 -4alkyl)aminosulfonyl;

25 R^7 is hydrogen or C_1 -6alkyl provided that the dotted line does not represent a bond;

R^8 is hydrogen, C_1 -6alkyl or Ar^2CH_2 or Het^1CH_2 ;

R^9 is hydrogen, C_1 -6alkyl, C_1 -6alkyloxy or halo; or

R^8 and R^9 taken together to form a bivalent radical of formula

$-CH=CH-$ (c-1),

30 $-CH_2-CH_2-$ (c-2),

$-CH_2-CH_2-CH_2-$ (c-3),

$-CH_2-O-$ (c-4), or

$-CH_2-CH_2-O-$ (c-5);

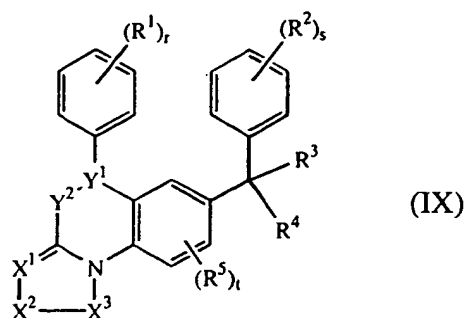
35 Ar^1 is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C_1 -6alkyl, C_1 -6alkyloxy or trifluoromethyl;

Ar² is phenyl; or phenyl substituted with 1 or 2 substituents each independently selected from halo, C₁-6alkyl, C₁-6alkyloxy or trifluoromethyl; and

Het¹ is pyridinyl; pyridinyl substituted with 1 or 2 substituents each independently selected from halo, C₁-6alkyl, C₁-6alkyloxy or trifluoromethyl.

5

WO-00/39082 concerns the preparation, formulation and pharmaceutical properties of farnesyl protein transferase inhibiting compounds of formula (IX)



10 or the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

=X¹-X²-X³- is a trivalent radical of formula

- | | | | |
|---------------------------------------|--------|--|-----------|
| =N-CR ⁶ =CR ⁷ - | (x-1), | =CR ⁶ -CR ⁷ =CR ⁸ - | (x-6), |
| =N-N=CR ⁶ - | (x-2), | =CR ⁶ -N=CR ⁷ - | (x-7), |
| 15 =N-NH-C(=O)- | (x-3), | =CR ⁶ -NH-C(=O)- | (x-8), or |
| =N-N=N- | (x-4), | =CR ⁶ -N=N- | (x-9); |
| =N-CR ⁶ =N- | (x-5), | | |

wherein each R⁶, R⁷ and R⁸ are independently hydrogen, C₁₋₄alkyl, hydroxy, C₁₋₄alkyloxy, aryloxy, C₁₋₄alkyloxycarbonyl, hydroxyC₁₋₄alkyl, C₁₋₄alkyloxyC₁₋₄alkyl, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, cyano, amino, thio, C₁₋₄alkylthio, arylthio or aryl;

20 >Y¹-Y²- is a trivalent radical of formula

- | | |
|--------------------------|-----------|
| >CH-CHR ⁹ - | (y-1), |
| >C=N- | (y-2), |
| 25 >CH-NR ⁹ - | (y-3), or |
| >C=CR ⁹ - | (y-4); |

wherein each R⁹ independently is hydrogen, halo, halocarbonyl, aminocarbonyl, hydroxyC₁₋₄alkyl, cyano, carboxyl, C₁₋₄alkyl, C₁₋₄alkyloxy, C₁₋₄alkyloxyC₁₋₄alkyl, C₁₋₄alkyloxycarbonyl, mono- or di(C₁₋₄alkyl)amino, mono- or di(C₁₋₄alkyl)aminoC₁₋₄alkyl, aryl;

30

r and s are each independently 0, 1, 2, 3, 4 or 5;

t is 0, 1, 2 or 3;

each R¹ and R² are independently hydroxy, halo, cyano, C₁₋₆alkyl, trihalomethyl, trihalomethoxy, C₂₋₆alkenyl, C₁₋₆alkyloxy, hydroxyC₁₋₆alkyloxy, C₁₋₆alkylthio, C₁₋₆alkyloxyC₁₋₆alkyloxy, C₁₋₆alkyloxycarbonyl, aminoC₁₋₆alkyloxy, mono- or di(C₁₋₆alkyl)amino, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyloxy, aryl, arylC₁₋₆alkyl, aryloxy or arylC₁₋₆alkyloxy, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, aminocarbonyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminocarbonyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl; or two R¹ or R² substituents adjacent to one another on the phenyl ring may independently form together a bivalent radical of formula

10 -O-CH₂-O- (a-1),

 -O-CH₂-CH₂-O- (a-2),

 -O=CH=CH- (a-3),

 -O-CH₂-CH₂- (a-4),

 -O-CH₂-CH₂-CH₂- (a-5), or

15 -CH=CH-CH=CH- (a-6);

R³ is hydrogen, halo, C₁₋₆alkyl, cyano, haloC₁₋₆alkyl, hydroxyC₁₋₆alkyl, cyanoC₁₋₆alkyl, aminoC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, hydroxycarbonyl, hydroxycarbonylC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, C₁₋₆alkylcarbonylC₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, aryl, arylC₁₋₆alkyloxyC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkyl;

or a radical of formula

 -O-R¹⁰ (b-1),

 -S-R¹⁰ (b-2),

 -NR¹¹R¹² (b-3),

25 wherein R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, aryl, arylC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, or a radical of formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵;

 R¹¹ is hydrogen, C₁₋₆alkyl, aryl or arylC₁₋₆alkyl;

 R¹² is hydrogen, C₁₋₆alkyl, aryl, hydroxy, amino, C₁₋₆alkyloxy, C₁₋₆alkylcarbonylC₁₋₆alkyl, arylC₁₋₆alkyl, C₁₋₆alkylcarbonylamino, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkylcarbonyl, aminocarbonyl, arylcarbonyl, haloC₁₋₆alkylcarbonyl, arylC₁₋₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, mono- or di(C₁₋₆alkyl)aminocarbonyl wherein the alkyl moiety may optionally be substituted by one or more substituents independently selected from aryl or C₁₋₃alkyloxycarbonyl, aminocarbonylcarbonyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, or a radical or formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵;

 wherein Alk is C₁₋₆alkanediyl;

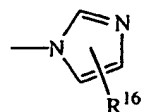
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R^{13} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, hydroxy C_{1-6} alkyl, aryl or aryl C_{1-6} alkyl;

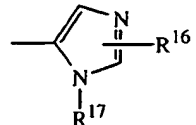
R^{14} is hydrogen, C_{1-6} alkyl, aryl or aryl C_{1-6} alkyl;

R^{15} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, aryl or aryl C_{1-6} alkyl;

5 R^4 is a radical of formula



(c-1),



(c-2),

wherein R^{16} is hydrogen, halo, aryl, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, mono- or di(C_{1-4} alkyl)amino, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylthio C_{1-6} alkyl,

10 C_{1-6} alkylS(O) C_{1-6} alkyl or C_{1-6} alkylS(O) $_2$ C_{1-6} alkyl;

R^{16} may also be bound to one of the nitrogen atoms in the imidazole ring of formula (c-1) or (c-2), in which case the meaning of R^{16} when bound to the nitrogen is limited to hydrogen, aryl, C_{1-6} alkyl, hydroxy C_{1-6} alkyl,

15 C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylS(O) C_{1-6} alkyl or C_{1-6} alkylS(O) $_2$ C_{1-6} alkyl;

R^{17} is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, aryl C_{1-6} alkyl, trifluoromethyl or di(C_{1-4} alkyl)aminosulfonyl;

R^5 is C_{1-6} alkyl, C_{1-6} alkyloxy or halo;

aryl is phenyl, naphthalenyl or phenyl substituted with 1 or more substituents each

20 independently selected from halo, C_{1-6} alkyl, C_{1-6} alkyloxy or trifluoromethyl.

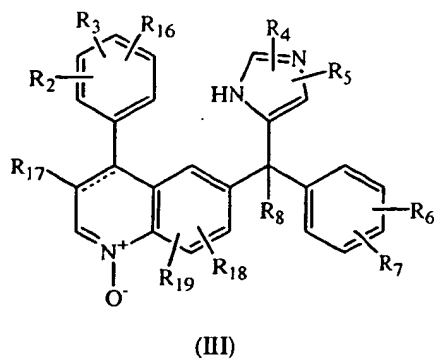
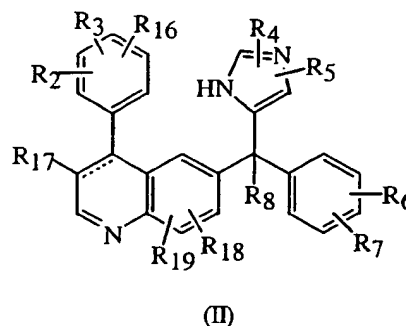
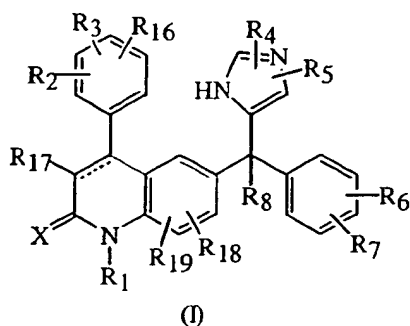
Amplification of the human epidermal growth factor receptor 2 protein (HER 2) in primary breast carcinomas has been shown to correlate with a poor clinical prognosis for certain patients. Trastuzumab is a highly purified recombinant DNA-derived humanized monoclonal IgG1 kappa antibody that binds with high affinity and specificity to the extracellular domain of the HER2 receptor. In vitro and in vivo preclinical studies have shown that administration of trastuzumab alone or in combination with paclitaxel or carboplatin significantly inhibits the growth of breast tumor-derived cell lines that over-express the HER2 gene product. In a clinical studies trastuzumab has been shown to have clinical activity in the treatment of breast cancer. The most common adverse effects attributed to trastuzumab in clinical studies were fever and chills, pain, asthenia, nausea, vomiting increased cough, diarrhea, headache, dyspnea, infection, rhinitis, and insomnia. Trastuzumab has been approved in the USA as single agent for the treatment of patients who have metastatic breast cancer involving over-expression of the HER2 protein and who have received one or more

chemotherapy regimes; in combination with paclitaxel, it has also been approved for the treatment of such patients who have not received chemotherapy.

There is therefore a need to increase the inhibitory efficacy of trastuzumab against tumor growth and also to provide a means for the use of lower dosages of trastuzumab to reduce the potential of adverse toxic side effects to the patient.

It is an object of the invention to provide a therapeutic combination of trastuzumab and a farnesyl transferase inhibitor of the type described above which has an advantageous inhibitory effect against tumor cell growth, in comparison with the respective effects shown by the individual components of the combination.

According to the invention therefore we provide a combination of trastuzumab and a farnesyl transferase inhibitor of formula (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) above, in particular a compound of formula (I), (II) or (III):



the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R^1 is hydrogen, C_{1-12} alkyl, Ar^1 , Ar^2C_{1-6} alkyl, quinoliny C_{1-6} alkyl, pyridyl- C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)-amino C_{1-6} alkyl, amino C_{1-6} alkyl,
 or a radical of formula $-Alk^1-C(=O)-R^9$, $-Alk^1-S(O)-R^9$ or $-Alk^1-S(O)_2-R^9$,
 5 wherein Alk^1 is C_{1-6} alkanediyl,

R^9 is hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy, amino, C_{1-8} alkylamino or
 C_{1-8} alkylamino substituted with C_{1-6} alkyloxycarbonyl;

R^2 , R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6} alkyl,
 C_{1-6} alkyloxy, hydroxy C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyloxy,
 10 amino C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, Ar^1 ,
 Ar^2C_{1-6} alkyl, Ar^2 oxy, Ar^2C_{1-6} alkyloxy, hydroxycarbonyl,
 C_{1-6} alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6} alkenyl, 4,4-
 dimethyloxazolyl; or
 when on adjacent positions R^2 and R^3 taken together may form a bivalent radical
 15 of formula

$-O-CH_2-O-$ (a-1),

$-O-CH_2-CH_2-O-$ (a-2),

$-O-CH=CH-$ (a-3),

$-O-CH_2-CH_2-$ (a-4),

20 $-O-CH_2-CH_2-CH_2-$ (a-5), or

$-CH=CH-CH=CH-$ (a-6);

R^4 and R^5 each independently are hydrogen, halo, Ar^1 , C_{1-6} alkyl, hydroxy C_{1-6} alkyl,
 C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, hydroxycarbonyl,
 C_{1-6} alkyloxycarbonyl, C_{1-6} alkylS(O) C_{1-6} alkyl or C_{1-6} alkylS(O) $_2C_{1-6}$ alkyl;

25 R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy,
 Ar^2 oxy, trihalomethyl, C_{1-6} alkylthio, di(C_{1-6} alkyl)amino, or
 when on adjacent positions R^6 and R^7 taken together may form a bivalent radical
 of formula

$-O-CH_2-O-$ (c-1), or

30 $-CH=CH-CH=CH-$ (c-2);

R^8 is hydrogen, C_{1-6} alkyl, cyano, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl-
 carbonyl C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, carboxy-
 C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino-
 C_{1-6} alkyl, imidazolyl, halo C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, aminocarbonyl-
 35 C_{1-6} alkyl, or a radical of formula

$-O-R^{10}$ (b-1),

$-S-R^{10}$ (b-2),

-15-

-N-R¹¹R¹² (b-3),

wherein R¹⁰ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹, Ar²C₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;

5 R¹¹ is hydrogen, C₁₋₁₂alkyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹² is hydrogen, C₁₋₆alkyl, C₁₋₁₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminocarbonyl, Ar¹, Ar²C₁₋₆alkyl, C₁₋₆alkylcarbonyl-C₁₋₆alkyl, a natural amino acid, Ar¹carbonyl, Ar²C₁₋₆alkylcarbonyl, aminocarbonylcarbonyl, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, hydroxy, C₁₋₆alkyloxy, aminocarbonyl, di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, amino, C₁₋₆alkylamino, C₁₋₆alkylcarbonylamino, or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵; wherein Alk² is C₁₋₆alkanediyl;

15 R¹³ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, hydroxy-C₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹⁴ is hydrogen, C₁₋₆alkyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹⁵ is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar¹ or Ar²C₁₋₆alkyl;

R¹⁷ is hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, Ar¹;

20 R¹⁸ is hydrogen, C₁₋₆alkyl, C₁₋₆alkyloxy or halo;

R¹⁹ is hydrogen or C₁₋₆alkyl;

Ar¹ is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo; and

25 Ar² is phenyl or phenyl substituted with C₁₋₆alkyl, hydroxy, amino, C₁₋₆alkyloxy or halo.

The above described combinations are hereinafter referred to as combinations according to the invention. These combinations may provide a synergistic effect whereby they demonstrate an advantageous therapeutic effect which is greater than that which would have been expected from the effects of the individual components of the combinations.

In Formulas (I), (II) and (III), R⁴ or R⁵ may also be bound to one of the nitrogen atoms in the imidazole ring. In that case the hydrogen on the nitrogen is replaced by R⁴ or R⁵ and the meaning of R⁴ and R⁵ when bound to the nitrogen is limited to hydrogen, Ar¹, C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylS(O)C₁₋₆alkyl, C₁₋₆alkylS(O)₂C₁₋₆alkyl.

Preferably the substituent R¹⁸ is situated on the 5 or 7 position of the quinolinone moiety and substituent R¹⁹ is situated on the 8 position when R¹⁸ is on the 7-position.

5 Interesting compounds are these compounds of formula (I) wherein X is oxygen.

Also interesting compounds are these compounds of formula (I) wherein the dotted line represents a bond, so as to form a double bond.

10 Another group of interesting compounds are those compounds of formula (I) wherein R¹ is hydrogen, C₁-6alkyl, C₁-6alkyloxyC₁-6alkyl, di(C₁-6alkyl)aminoC₁-6alkyl, or a radical of formula -Alk¹-C(=O)-R⁹, wherein Alk¹ is methylene and R⁹ is C₁-8alkyl-amino substituted with C₁-6alkyloxycarbonyl.

15 Still another group of interesting compounds are those compounds of formula (I) wherein R³ is hydrogen or halo; and R² is halo, C₁-6alkyl, C₂-6alkenyl, C₁-6alkyloxy, trihalomethoxy or hydroxyC₁-6alkyloxy.

A further group of interesting compounds are those compounds of formula (I) wherein
20 R² and R³ are on adjacent positions and taken together to form a bivalent radical of formula (a-1), (a-2) or (a-3).

A still further group of interesting compounds are those compounds of formula (I) wherein R⁵ is hydrogen and R⁴ is hydrogen or C₁-6alkyl.

25 Yet another group of interesting compounds are those compounds of formula (I) wherein R⁷ is hydrogen; and R⁶ is C₁-6alkyl or halo, preferably chloro, especially 4-chloro.

30 A particular group of compounds are those compounds of formula (I) wherein R⁸ is hydrogen, hydroxy, haloC₁-6alkyl, hydroxyC₁-6alkyl, cyanoC₁-6alkyl, C₁-6alkyloxy-carbonylC₁-6alkyl, imidazolyl, or a radical of formula -NR¹¹R¹² wherein R¹¹ is hydrogen or C₁-12alkyl and R¹² is hydrogen, C₁-6alkyl, C₁-6alkyloxy, hydroxy, C₁-6alkyloxyC₁-6alkylcarbonyl, or a radical of formula -Alk²-OR¹³ wherein R¹³ is
35 hydrogen or C₁-6alkyl.

Preferred compounds are those compounds wherein R^1 is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, di(C_{1-6} alkyl)amino C_{1-6} alkyl, or a radical of formula $-Alk^1-C(=O)-R^9$, wherein Alk^1 is methylene and R^9 is C_{1-8} alkylamino substituted with C_{1-6} alkyloxycarbonyl; R^2 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, trihalo-methoxy, hydroxy C_{1-6} alkyloxy or Ar^1 ; R^3 is hydrogen; R^4 is methyl bound to the nitrogen in 3-position of the imidazole; R^5 is hydrogen; R^6 is chloro; R^7 is hydrogen; R^8 is hydrogen, hydroxy, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, imidazolyl, or a radical of formula $-NR^{11}R^{12}$ wherein R^{11} is hydrogen or C_{1-12} alkyl and R^{12} is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkylcarbonyl, or a radical of formula $-Alk^2-OR^{13}$ wherein R^{13} is C_{1-6} alkyl; R^{17} is hydrogen and R^{18} is hydrogen.

Most preferred compounds are

4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-2(1*H*)-quinolinone,

6-[amino(4-chlorophenyl)-1-methyl-1*H*-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone;

6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone;

6-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone monohydrochloride monohydrate;

6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone,

6-amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1*H*)-quinolinone; a stereoisomeric form thereof or a pharmaceutically acceptable acid or base addition salt; and

(+)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone (Compound 75 in Table 1 of the Experimental part of WO-97/21701); or a pharmaceutically acceptable acid addition salt thereof. The latter compound is especially preferred.

Further preferred embodiments of the present invention include compounds of formula (IX) wherein one or more of the following restrictions apply:

- $=X^1-X^2-X^3$ is a trivalent radical of formula (x-1), (x-2), (x-3), (x-4) or (x-9) wherein each R^6 independently is hydrogen, C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl, amino or aryl and R^7 is hydrogen;

- $>Y^1-Y^2-$ is a trivalent radical of formula (y-1), (y-2), (y-3), or (y-4) wherein each R^9 independently is hydrogen, halo, carboxyl, C_{1-4} alkyl or C_{1-4} alkyloxycarbonyl;
- r is 0, 1 or 2;
- s is 0 or 1;
- 5 • t is 0;
- R^1 is halo, C_{1-6} alkyl or two R^1 substituents ortho to one another on the phenyl ring may independently form together a bivalent radical of formula (a-1);
- R^2 is halo;
- R^3 is halo or a radical of formula (b-1) or (b-3) wherein
- 10 R^{10} is hydrogen or a radical of formula $-Alk-OR^{13}$.
- R^{11} is hydrogen;
- R^{12} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, hydroxy, C_{1-6} alkyloxy or mono- or di(C_{1-6} alkyl)amino C_{1-6} alkylcarbonyl;
- Alk is C_{1-6} alkanediyl and R^{13} is hydrogen;
- 15 • R^4 is a radical of formula (c-1) or (c-2) wherein
- R^{16} is hydrogen, halo or mono- or di(C_{1-4} alkyl)amino;
- R^{17} is hydrogen or C_{1-6} alkyl;
- aryl is phenyl.

- 20 A particular group of compounds consists of those compounds of formula (IX) wherein $=X^1-X^2-X^3$ is a trivalent radical of formula (x-1), (x-2), (x-3), (x-4) or (x-9), $>Y^1-Y^2$ is a trivalent radical of formula (y-2), (y-3) or (y-4), r is 0 or 1, s is 1, t is 0, R^1 is halo, $C_{(1-4)}$ alkyl or forms a bivalent radical of formula (a-1), R^2 is halo or C_{1-4} alkyl, R^3 is hydrogen or a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-1) or (c-2),
- 25 R^6 is hydrogen, C_{1-4} alkyl or phenyl, R^7 is hydrogen, R^9 is hydrogen or C_{1-4} alkyl, R^{10} is hydrogen or $-Alk-OR^{13}$, R^{11} is hydrogen and R^{12} is hydrogen or C_{1-6} alkylcarbonyl and R^{13} is hydrogen;

- Preferred compounds are those compounds of formula (IX) wherein $=X^1-X^2-X^3$ is a
- 30 trivalent radical of formula (x-1) or (x-4), $>Y^1-Y^2$ is a trivalent radical of formula (y-4), r is 0 or 1, s is 1, t is 0, R^1 is halo, preferably chloro and most preferably 3-chloro, R^2 is halo, preferably 4-chloro or 4-fluoro, R^3 is hydrogen or a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-1) or (c-2), R^6 is hydrogen, R^7 is hydrogen, R^9 is hydrogen, R^{10} is hydrogen, R^{11} is hydrogen and R^{12} is hydrogen;

35

Other preferred compounds are those compounds of formula (IX) wherein $=X^1-X^2-X^3$ is a trivalent radical of formula (x-2), (x-3) or (x-4), $>Y^1-Y^2$ is a trivalent radical of formula (y-2), (y-3) or (y-4), r and s are 1, t is 0, R^1 is halo, preferably chloro, and most

preferably 3-chloro or R^1 is C_{1-4} alkyl, preferably 3-methyl, R^2 is halo, preferably chloro, and most preferably 4-chloro, R^3 is a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-2), R^6 is C_{1-4} alkyl, R^9 is hydrogen, R^{10} and R^{11} are hydrogen and R^{12} is hydrogen or hydroxy.

5

The most preferred compounds of formula (IX) are

7-[(4-fluorophenyl)(1H-imidazol-1-yl)methyl]-5-phenylimidazo[1,2-a]quinoline;
 α -(4-chlorophenyl)- α -(1-methyl-1H-imidazol-5-yl)-5-phenylimidazo[1,2-a]quinoline-7-methanol;

10 5-(3-chlorophenyl)- α -(4-chlorophenyl)- α -(1-methyl-1H-imidazol-5-yl)-imidazo[1,2-a]quinoline-7-methanol;

5-(3-chlorophenyl)- α -(4-chlorophenyl)- α -(1-methyl-1H-imidazol-5-yl)imidazo[1,2-a]quinoline-7-methanamine;

15 5-(3-chlorophenyl)- α -(4-chlorophenyl)- α -(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinoline-7-methanamine;

5-(3-chlorophenyl)- α -(4-chlorophenyl)-1-methyl- α -(1-methyl-1H-imidazol-5-yl)-1,2,4-triazolo[4,3-a]quinoline-7-methanol;

5-(3-chlorophenyl)- α -(4-chlorophenyl)- α -(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinoline-7-methanamine;

20 5-(3-chlorophenyl)- α -(4-chlorophenyl)- α -(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanol;

5-(3-chlorophenyl)- α -(4-chlorophenyl)-4,5-dihydro- α -(1-methyl-1H-imidazol-5-yl)-tetrazolo[1,5-a]quinazoline-7-methanol;

25 5-(3-chlorophenyl)- α -(4-chlorophenyl)- α -(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanamine;

5-(3-chlorophenyl)- α -(4-chlorophenyl)-N-hydroxy- α -(1-methyl-1H-imidazol-5-yl)-tetrahydro[1,5-a]quinoline-7-methanamine;

α -(4-chlorophenyl)- α -(1-methyl-1H-imidazol-5-yl)-5-(3-methylphenyl)tetrazolo[1,5-a]quinoline-7-methanamine; the pharmaceutically acceptable acid addition salts

30 and the stereochemically isomeric forms thereof.

5-(3-chlorophenyl)- α -(4-chlorophenyl)- α -(1-methyl-1H-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanamine, especially the (-) enantiomer, and its pharmaceutically acceptable acid addition salts are especially preferred.

35

As used in the foregoing definitions and hereinafter halo defines fluoro, chloro, bromo and iodo; C_{1-6} alkyl defines straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms such as, for example, methyl, ethyl, propyl,

butyl, pentyl, hexyl and the like; C₁-8alkyl encompasses the straight and branched chained saturated hydrocarbon radicals as defined in C₁-6alkyl as well as the higher homologues thereof containing 7 or 8 carbon atoms such as, for example heptyl or octyl; C₁-12alkyl again encompasses C₁-8alkyl and the higher homologues thereof containing 9 to 12 carbon atoms, such as, for example, nonyl, decyl, undecyl, dodecyl; C₁-16alkyl again encompasses C₁-12alkyl and the higher homologues thereof containing 13 to 16 carbon atoms, such as, for example, tridecyl, tetradecyl, pentadecyl and hexadecyl; C₂-6alkenyl defines straight and branched chain hydrocarbon radicals containing one double bond and having from 2 to 6 carbon atoms such as, for example, ethenyl, 2-propenyl, 3-butenyl, 2-pentenyl, 3-pentenyl, 3-methyl-2-butenyl, and the like; C₁-6alkanediyl defines bivalent straight and branched chained saturated hydrocarbon radicals having from 1 to 6 carbon atoms, such as, for example, methylene, 1,2-ethanediyl, 1,3-propanediyl, 1,4-butanediyl, 1,5-pentanediyl, 1,6-hexanediyl and the branched isomers thereof. The term "C(=O)" refers to a carbonyl group, "S(O)" refers to a sulfoxide and "S(O)₂" to a sulfon. The term "natural amino acid" refers to a natural amino acid that is bound via a covalent amide linkage formed by loss of a molecule of water between the carboxyl group of the amino acid and the amino group of the remainder of the molecule. Examples of natural amino acids are glycine, alanine, valine, leucine, isoleucine, methionine, proline, phenylalanine, tryptophan, serine, threonine, cysteine, tyrosine, asparagine, glutamine, aspartic acid, glutamic acid, lysine, arginine, histidine.

The pharmaceutically acceptable acid or base addition salts as mentioned hereinabove are meant to comprise the therapeutically active non-toxic acid and non-toxic base addition salt forms which the compounds of formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) are able to form. The compounds of formulas (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) which have basic properties can be converted in their pharmaceutically acceptable acid addition salts by treating said base form with an appropriate acid. Appropriate acids comprise, for example, inorganic acids such as hydrohalic acids, e.g. hydrochloric or hydrobromic acid; sulfuric; nitric; phosphoric and the like acids; or organic acids such as, for example, acetic, propanoic, hydroxyacetic, lactic, pyruvic, oxalic, malonic, succinic (i.e. butanedioic acid), maleic, fumaric, malic, tartaric, citric, methanesulfonic, ethanesulfonic, benzenesulfonic, p-toluenesulfonic, cyclamic, salicylic, p-aminosalicylic, pamoic and the like acids.

The compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) which have acidic properties may be converted in their pharmaceutically acceptable base addition salts by treating said acid form with a suitable organic or inorganic base.

Appropriate base salt forms comprise, for example, the ammonium salts, the alkali and earth alkaline metal salts, e.g. the lithium, sodium, potassium, magnesium, calcium salts and the like, salts with organic bases, e.g. the benzathine, N-methyl-D-glucamine, hydrabamine salts, and salts with amino acids such as, for example, arginine, lysine and the like.

The terms acid or base addition salt also comprise the hydrates and the solvent addition forms which the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) are able to form. Examples of such forms are e.g. hydrates, alcoholates and the like.

The term stereochemically isomeric forms of compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX), as used hereinbefore, defines all possible compounds made up of the same atoms bonded by the same sequence of bonds but having different three-dimensional structures which are not interchangeable, which the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) may possess. Unless otherwise mentioned or indicated, the chemical designation of a compound encompasses the mixture of all possible stereochemically isomeric forms which said compound may possess. Said mixture may contain all diastereomers and/or enantiomers of the basic molecular structure of said compound. All stereochemically isomeric forms of the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) both in pure form or in admixture with each other are intended to be embraced within the scope of the present invention.

Some of the compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX) may also exist in their tautomeric forms. Such forms although not explicitly indicated in the above formula are intended to be included within the scope of the present invention.

Whenever used hereinafter, the term "compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) or (IX)" is meant to include also the pharmaceutically acceptable acid or base addition salts and all stereoisomeric forms.

Trastuzumab is commercially available from Genentech under the trade name Herceptin and may be obtained as described in U.S. Patent specification No. 5821337 or PCT patent specifications WO 94/04679 and WO 92/22653.

The present invention also relates to combinations according to the invention for use in medical therapy for example for inhibiting the growth of tumor cells.

5 The present invention also relates to the use of combinations according to the invention for the preparation of a pharmaceutical composition for inhibiting the growth of tumor cells.

10 The present invention also relates to a method of inhibiting the growth of tumor cells in a human subject which comprises administering to the subject an effective amount of a combination according to the invention.

This invention further provides a method for inhibiting the abnormal growth of cells, including transformed cells, by administering an effective amount of a combination according to the invention. Abnormal growth of cells refers to cell growth independent of normal regulatory mechanisms (e.g. loss of contact inhibition). This includes the abnormal growth of : (1) tumor cells (tumors) expressing an activated ras oncogene; (2) tumor cells in which the ras protein is activated as a result of oncogenic mutation of another gene; (3) benign and malignant cells of other proliferative diseases in which aberrant ras activation occurs. Furthermore, it has been suggested in literature that ras oncogenes not only contribute to the growth of of tumors in vivo by a direct effect on tumor cell growth but also indirectly, i.e. by facilitating tumor-induced angiogenesis (Rak. J. et al, Cancer Research, 55, 4575-4580, 1995). Hence, pharmacologically targetting mutant ras oncogenes could conceivably suppress solid tumor growth in vivo, in part, by inhibiting tumor-induced angiogenesis.

25 This invention also provides a method for inhibiting tumor growth by administering an effective amount of a combination according to the present invention, to a subject, e.g. a mammal (and more particularly a human) in need of such treatment. In particular, this invention provides a method for inhibiting the growth of tumors expressing an activated ras oncogene by the administration of an effective amount of combination according to the present invention. Examples of tumors which may be inhibited include, but are not limited to, lung cancer (e.g. adenocarcinoma and including small cell lung cancer), pancreatic cancers (e.g. pancreatic carcinoma such as, for example exocrine pancreatic carcinoma), colon cancers (e.g. colorectal carcinomas, such as, for example, colon adenocarcinoma and colon adenoma), hematopoietic tumors of lymphoid lineage (e.g. acute lymphocytic leukemia, B-cell lymphoma, Burkitt's lymphoma), myeloid leukemias (for example, acute myelogenous leukemia (AML)), thyroid follicular cancer, myelodysplastic syndrome (MDS), tumors of mesenchymal

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origin (e.g. fibrosarcomas and rhabdomyosarcomas), melanomas, teratocarcinomas, neuroblastomas, gliomas, benign tumor of the skin (e.g. keratoacanthomas), breast carcinoma (e.g. advanced breast cancer), kidney carcinoma, ovary carcinoma, bladder carcinoma and epidermal carcinoma.

5

This invention also provides a method for inhibiting proliferative diseases, both benign and malignant, wherein ras proteins are aberrantly activated as a result of oncogenic mutation in genes, i.e. the ras gene itself is not activated by mutation to an oncogenic mutation to an oncogenic form, with said inhibition being accomplished by the
10 administration of an effective amount of a combination according to the invention, to a subject in need of such a treatment. For example, the benign proliferative disorder neurofibromatosis, or tumors in which ras is activated due to mutation or overexpression of tyrosine kinase oncogenes may be inhibited by the combinations according to the invention.

15

The trastuzumab and the farnesyl transferase inhibitor may be administered simultaneously (e.g. in separate or unitary compositions) or sequentially in either order. In the latter case, the two compounds will be administered within a period and in an amount and manner that is sufficient to ensure that an advantageous or synergistic
20 effect is achieved. It will be appreciated that the preferred method and order of administration and the respective dosage amounts and regimes for each component of the combination will depend on the particular farnesyl transferase inhibitor being administered, their route of administration, the particular tumor being treated and the particular host being treated. The optimum method and order of administration and the
25 dosage amounts and regime can be readily determined by those skilled in the art using conventional methods and in view of the information set out herein.

The farnesyl transferase inhibitor is advantageously administered in an effective amount of from 0.0001 mg/kg to 100 mg/kg body weight, and in particular from 0.001
30 mg/kg to 10 mg/kg body weight. More particularly, for an adult patient, the dosage is conveniently in the range of 50 to 500mg bid, advantageously 100 to 400 mg bid and particularly 300mg bid.

Trastuzumab is advantageously administered in a dosage of 1 to 5mg per square meter
35 (mg/m²) of body surface area, particularly 2 to 4mg/m² per course of treatment. These dosages may be administered for example once, twice or more per course of treatment, which may be repeated for example every 7, 14, 21 or 28 days.

It is especially preferred to administer the farnesyl transferase inhibitor at a dosage of 100 or 200mg bid for 7, 14, 21 or 28 days with a dosage of the trastuzumab in the ranges indicated above.

- 5 In view of their useful pharmacological properties, the components of the combinations according to the invention, i.e. the trastuzumab and the farnesyl transferase inhibitor may be formulated into various pharmaceutical forms for administration purposes. The components may be formulated separately in individual pharmaceutical compositions or in a unitary pharmaceutical composition containing both components. Farnesyl protein
- 10 transferase inhibitors can be prepared and formulated into pharmaceutical compositions by methods known in the art and in particular according to the methods described in the published patent specifications mentioned herein and incorporated by reference; for the compounds of formulae (I), (II) and (III) suitable examples can be found in WO 97/21701. Compounds of formulae (IV), (V), and (VI) can be prepared and
- 15 formulated using methods described in WO 97/16443, compounds of formulae (VII) and (VIII) according to methods described in WO 98/40383 and WO 98/49157 and compounds of formula (IX) according to methods described in WO 00/39082 respectively.
- 20 The present invention therefore also relates to a pharmaceutical composition comprising trastuzumab and a farnesyl transferase inhibitor of formula (I) together with one or more pharmaceutical carriers. To prepare pharmaceutical compositions for use in accordance with the invention, an effective amount of a particular compound, in base or acid addition salt form, as the active ingredient is combined in intimate
- 25 admixture with a pharmaceutically acceptable carrier, which carrier may take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, preferably, for administration orally, rectally, percutaneously, or by parenteral injection. For example, in preparing the compositions in oral dosage form, any of the
- 30 usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in administration, tablets and capsules
- 35 represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, to aid solubility for example, may be included. Injectable solutions, for

example, may be prepared in which the carrier comprises saline solution, glucose solution or a mixture of saline and glucose solution. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed. In the compositions suitable for percutaneous administration, the carrier
5 optionally comprises a penetration enhancing agent and/or a suitable wetting agent, optionally combined with suitable additives of any nature in minor proportions, which additives do not cause a significant deleterious effect to the skin. Said additives may facilitate the administration to the skin and/or may be helpful for preparing the desired compositions. These compositions may be administered in various ways, e.g., as a
10 transdermal patch, as a spot-on, as an ointment.

It is especially advantageous to formulate the aforementioned pharmaceutical compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used in the specification and claims herein refers to physically
15 discrete units suitable as unitary dosages, each unit containing a predetermined quantity of active ingredient calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier. Examples of such dosage unit forms are tablets (including scored or coated tablets), capsules, pills, powder packets, wafers, injectable solutions or suspensions, teaspoonfuls, tablespoonfuls and the like, and
20 segregated multiples thereof.

It may be appropriate to administer the required dose of each component of the combination as two, three, four or more sub-doses at appropriate intervals throughout the course of treatment. Said sub-doses may be formulated as unit dosage forms, for
25 example, in each case containing independently 0.01 to 500 mg, for example 0.1 to 200 mg and in particular 1 to 100mg of each active ingredient per unit dosage form.

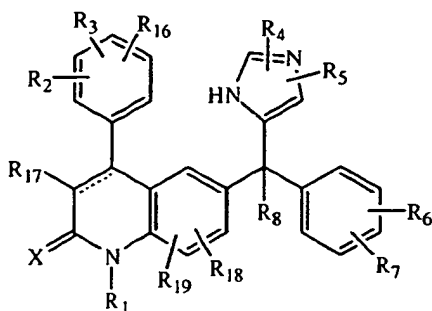
Experimental Testing of Combinations for Inhibition of Tumor Growth

30 The combinations according to the invention may be tested for their efficacy in inhibiting tumor growth using conventional assays described in the literature for example the HTB177 lung carcinoma described by Liu M et al, Cancer Research, Vol. 58, No.21, 1 November 1998, pages 4947-4956, and the anti-mitotic assay described by Moasser M et al, Proc. Natl. Acad. Sci. USA, Vol. 95, pages 1369-1374, February
35 1998. Other *in vitro* and *in vivo* models for determining ant-tumor effects of combinations and possible synergy of the combinations according to the invention are described in WO 98/54966 and WO 98/32114. Clinical models for determining the efficacy and possible synergism for combination therapy in the clinic are generally

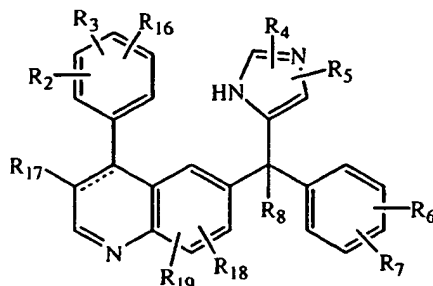
described in Cancer: Principles and Practice of Oncology, Fifth Edition, edited by Vincent T DeVita, Jr., Samuel Hellman, Steven A. Rosenberg, Lippincott-Raven, Philadelphia, 1997, especially Chapter 17, pages 342-346.

Claims

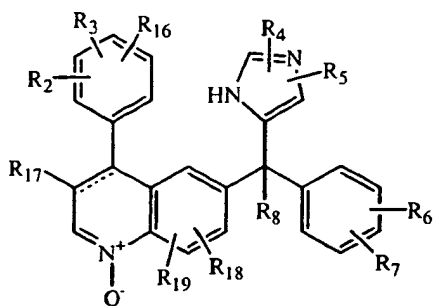
1. A combination of trastuzumab and a farnesyl transferase inhibitor selected from compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII), (VIII) and (IX) below:



(I)



(II)



(III)

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the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

- 10 R^1 is hydrogen, C_{1-12} alkyl, Ar^1 , Ar^2C_{1-6} alkyl, quinolinyl C_{1-6} alkyl, pyridyl- C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl, amino C_{1-6} alkyl, or a radical of formula $-Alk^1-C(=O)-R^9$, $-Alk^1-S(O)-R^9$ or $-Alk^1-S(O)_2-R^9$, wherein Alk^1 is C_{1-6} alkanediyl,

- 15 R^9 is hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy, amino, C_{1-8} alkylamino or C_{1-8} alkylamino substituted with C_{1-6} alkyloxycarbonyl;

R^2 , R^3 and R^{16} each independently are hydrogen, hydroxy, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyloxy, amino C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, Ar^1 , Ar^2C_{1-6} alkyl, Ar^2 oxy, Ar^2C_{1-6} alkyloxy, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6} alkenyl, 4,4-dimethyloxazolyl; or

20

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical of formula

- O-CH₂-O- (a-1),
- O-CH₂-CH₂-O- (a-2),
- O-CH=CH- (a-3),
- O-CH₂-CH₂- (a-4),
- O-CH₂-CH₂-CH₂- (a-5), or
- CH=CH-CH=CH- (a-6);

R^4 and R^5 each independently are hydrogen, halo, Ar^1 , C₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, C₁₋₆alkyloxy, C₁₋₆alkylthio, amino, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylS(O)C₁₋₆alkyl or C₁₋₆alkylS(O)₂C₁₋₆alkyl;

R^6 and R^7 each independently are hydrogen, halo, cyano, C₁₋₆alkyl, C₁₋₆alkyloxy, Ar^2 oxy, trihalomethyl, C₁₋₆alkylthio, di(C₁₋₆alkyl)amino, or when on adjacent positions R^6 and R^7 taken together may form a bivalent radical of formula

- O-CH₂-O- (c-1), or
- CH=CH-CH=CH- (c-2);

R^8 is hydrogen, C₁₋₆alkyl, cyano, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylcarbonylC₁₋₆alkyl, cyanoC₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, carboxyC₁₋₆alkyl, hydroxyC₁₋₆alkyl, aminoC₁₋₆alkyl, mono- or di(C₁₋₆alkyl)-aminoC₁₋₆alkyl, imidazolyl, haloC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, aminocarbonylC₁₋₆alkyl, or a radical of formula

- O-R¹⁰ (b-1),
- S-R¹⁰ (b-2),
- N-R¹¹R¹² (b-3),

wherein R^{10} is hydrogen, C₁₋₆alkyl, C₁₋₆alkylcarbonyl, Ar^1 , Ar^2 C₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;

R^{11} is hydrogen, C₁₋₁₂alkyl, Ar^1 or Ar^2 C₁₋₆alkyl;

R^{12} is hydrogen, C₁₋₆alkyl, C₁₋₁₆alkylcarbonyl, C₁₋₆alkyloxycarbonyl, C₁₋₆alkylaminocarbonyl, Ar^1 , Ar^2 C₁₋₆alkyl, C₁₋₆alkylcarbonyl-C₁₋₆alkyl, a natural amino acid, Ar^1 carbonyl, Ar^2 C₁₋₆alkylcarbonyl, aminocarbonylcarbonyl, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, hydroxy, C₁₋₆alkyloxy, aminocarbonyl, di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, amino, C₁₋₆alkylamino, C₁₋₆alkylcarbonylamino, or a radical or formula -Alk²-OR¹³ or -Alk²-NR¹⁴R¹⁵;

wherein Alk² is C₁₋₆alkanediyl;

-29-

R¹³ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, hydroxy-C₁-6alkyl, Ar¹ or Ar²C₁-6alkyl;

R¹⁴ is hydrogen, C₁-6alkyl, Ar¹ or Ar²C₁-6alkyl;

R¹⁵ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar¹ or Ar²C₁-6alkyl;

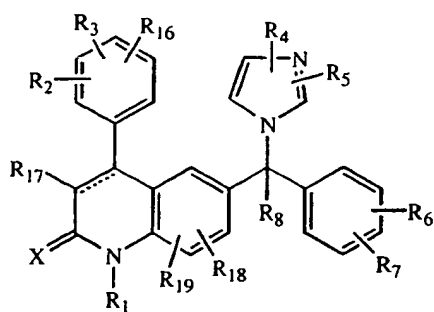
R¹⁷ is hydrogen, halo, cyano, C₁-6alkyl, C₁-6alkyloxy, Ar¹;

R¹⁸ is hydrogen, C₁-6alkyl, C₁-6alkyloxy or halo;

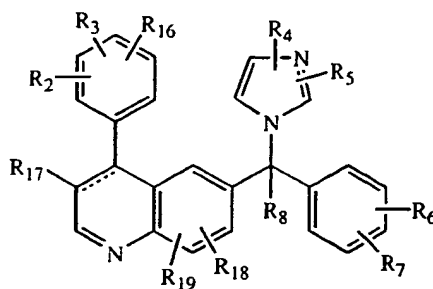
R¹⁹ is hydrogen or C₁-6alkyl;

Ar¹ is phenyl or phenyl substituted with C₁-6alkyl, hydroxy, amino, C₁-6alkyloxy or halo; and

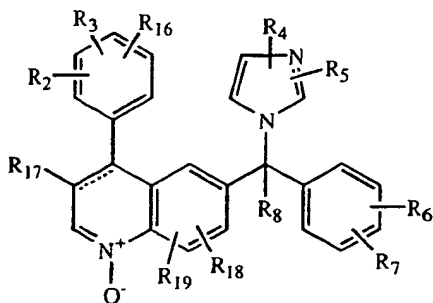
Ar² is phenyl or phenyl substituted with C₁-6alkyl, hydroxy, amino, C₁-6alkyloxy or halo.



(IV)



(V)



(VI)

the pharmaceutically acceptable acid or base addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

X is oxygen or sulfur;

R¹ is hydrogen, C₁-12alkyl, Ar¹, Ar²C₁-6alkyl, quinolinylC₁-6alkyl, pyridyl-C₁-6alkyl, hydroxyC₁-6alkyl, C₁-6alkyloxyC₁-6alkyl, mono- or di(C₁-6alkyl)-aminoC₁-6alkyl, aminoC₁-6alkyl,

or a radical of formula -Alk¹-C(=O)-R⁹, -Alk¹-S(O)-R⁹ or -Alk¹-S(O)₂-R⁹,

wherein Alk^1 is C_{1-6} alkanediyl,

R^9 is hydroxy, C_{1-6} alkyl, C_{1-6} alkyloxy, amino, C_{1-6} alkylamino or C_{1-6} alkylamino substituted with C_{1-6} alkyloxycarbonyl;

R^2 and R^3 each independently are hydrogen, hydroxy, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyloxy, amino-
 5 C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, Ar^1 , $\text{Ar}^2\text{C}_{1-6}$ alkyl, Ar^2oxy , $\text{Ar}^2\text{C}_{1-6}$ alkyloxy, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, trihalomethyl, trihalomethoxy, C_{2-6} alkenyl; or

when on adjacent positions R^2 and R^3 taken together may form a bivalent radical
 10 of formula

$-\text{O}-\text{CH}_2-\text{O}-$ (a-1),

$-\text{O}-\text{CH}_2-\text{CH}_2-\text{O}-$ (a-2),

$-\text{O}-\text{CH}=\text{CH}-$ (a-3),

$-\text{O}-\text{CH}_2-\text{CH}_2-$ (a-4),

15 $-\text{O}-\text{CH}_2-\text{CH}_2-\text{CH}_2-$ (a-5), or

$-\text{CH}=\text{CH}-\text{CH}=\text{CH}-$ (a-6);

R^4 and R^5 each independently are hydrogen, Ar^1 , C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylS(O) C_{1-6} alkyl or C_{1-6} alkylS(O) $_2\text{C}_{1-6}$ alkyl;

20 R^6 and R^7 each independently are hydrogen, halo, cyano, C_{1-6} alkyl, C_{1-6} alkyloxy or Ar^2oxy ;

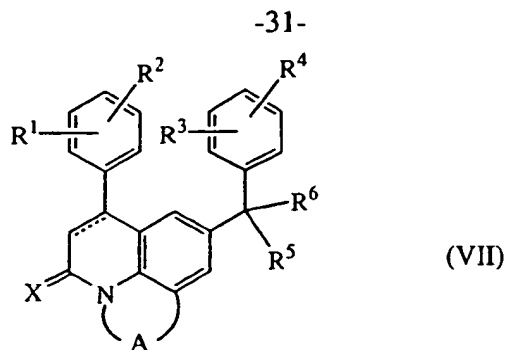
R^8 is hydrogen, C_{1-6} alkyl, cyano, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyl-carbonyl C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, hydroxy-carbonyl C_{1-6} alkyl, hydroxy C_{1-6} alkyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)-
 25 amino C_{1-6} alkyl, halo C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, aminocarbonyl C_{1-6} alkyl, Ar^1 , $\text{Ar}^2\text{C}_{1-6}$ alkyloxy C_{1-6} alkyl, C_{1-6} alkylthio C_{1-6} alkyl;

R^{10} is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy or halo;

R^{11} is hydrogen or C_{1-6} alkyl;

Ar^1 is phenyl or phenyl substituted with C_{1-6} alkyl, hydroxy, amino, C_{1-6} alkyloxy or
 30 halo;

Ar^2 is phenyl or phenyl substituted with C_{1-6} alkyl, hydroxy, amino, C_{1-6} alkyloxy or halo.



the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

5 X is oxygen or sulfur;

-A- is a bivalent radical of formula

- | | | | |
|--|--------|---------------------------------------|-----------|
| -CH=CH- | (a-1), | -CH ₂ -S- | (a-6), |
| -CH ₂ -CH ₂ - | (a-2), | -CH ₂ -CH ₂ -S- | (a-7), |
| -CH ₂ -CH ₂ -CH ₂ - | (a-3), | -CH=N- | (a-8), |
| 10 -CH ₂ -O- | (a-4), | -N=N- | (a-9), or |
| -CH ₂ -CH ₂ -O- | (a-5), | -CO-NH- | (a-10); |

wherein optionally one hydrogen atom may be replaced by C₁-4alkyl or Ar¹;

R¹ and R² each independently are hydrogen, hydroxy, halo, cyano, C₁-6alkyl, trihalomethyl, trihalomethoxy, C₂-6alkenyl, C₁-6alkyloxy, hydroxyC₁-6alkyloxy, C₁-6alkyloxyC₁-6alkyloxy, C₁-6alkyloxycarbonyl, aminoC₁-6alkyloxy, mono- or
 15 di(C₁-6alkyl)aminoC₁-6alkyloxy, Ar², Ar²-C₁-6alkyl, Ar²-oxy, Ar²-C₁-6alkyloxy; or when on adjacent positions R¹ and R² taken together may form a bivalent radical of formula

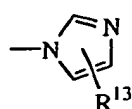
- | | |
|--|-----------|
| -O-CH ₂ -O- | (b-1), |
| 20 -O-CH ₂ -CH ₂ -O- | (b-2), |
| -O-CH=CH- | (b-3), |
| -O-CH ₂ -CH ₂ - | (b-4), |
| -O-CH ₂ -CH ₂ -CH ₂ - | (b-5), or |
| -CH=CH-CH=CH- | (b-6); |

25 R³ and R⁴ each independently are hydrogen, halo, cyano, C₁-6alkyl, C₁-6alkyloxy, Ar³-oxy, C₁-6alkylthio, di(C₁-6alkyl)amino, trihalomethyl, trihalomethoxy, or when on adjacent positions R³ and R⁴ taken together may form a bivalent radical of formula

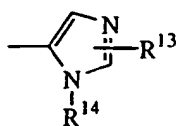
- | | |
|--|-----------|
| -O-CH ₂ -O- | (c-1), |
| 30 -O-CH ₂ -CH ₂ -O- | (c-2), or |
| -CH=CH-CH=CH- | (c-3); |

R⁵ is a radical of formula

-32-



(d-1),



(d-2),

wherein R^{13} is hydrogen, halo, Ar^4 , C_1 -6alkyl, hydroxy C_1 -6alkyl, C_1 -6alkyloxy- C_1 -6alkyl, C_1 -6alkyloxy, C_1 -6alkylthio, amino, C_1 -6alkyloxy-carbonyl, C_1 -6alkylS(O) C_1 -6alkyl or C_1 -6alkylS(O) $_2$ C_1 -6alkyl;

5 R^{14} is hydrogen, C_1 -6alkyl or di(C_1 -4alkyl)aminosulfonyl;

R^6 is hydrogen, hydroxy, halo, C_1 -6alkyl, cyano, halo C_1 -6alkyl, hydroxy C_1 -6alkyl, cyano C_1 -6alkyl, amino C_1 -6alkyl, C_1 -6alkyloxy C_1 -6alkyl, C_1 -6alkylthio C_1 -6alkyl, aminocarbonyl C_1 -6alkyl, C_1 -6alkyloxycarbonyl C_1 -6alkyl, C_1 -6alkylcarbonyl- C_1 -6alkyl, C_1 -6alkyloxycarbonyl, mono- or di(C_1 -6alkyl)amino C_1 -6alkyl, Ar^5 , Ar^5 - C_1 -6alkyloxy C_1 -6alkyl; or a radical of formula

-O- R^7 (e-1),

-S- R^7 (e-2),

-N- R^8R^9 (e-3),

15 wherein R^7 is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, Ar^6 , Ar^6 - C_1 -6alkyl, C_1 -6alkyloxycarbonyl C_1 -6alkyl, or a radical of formula -Alk-OR¹⁰ or -Alk-NR¹¹R¹²;

R^8 is hydrogen, C_1 -6alkyl, Ar^7 or Ar^7 - C_1 -6alkyl;

20 R^9 is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, C_1 -6alkyloxycarbonyl, C_1 -6alkylaminocarbonyl, Ar^8 , Ar^8 - C_1 -6alkyl, C_1 -6alkylcarbonyl- C_1 -6alkyl, Ar^8 -carbonyl, Ar^8 - C_1 -6alkylcarbonyl, aminocarbonyl-carbonyl, C_1 -6alkyloxy C_1 -6alkylcarbonyl, hydroxy, C_1 -6alkyloxy, aminocarbonyl, di(C_1 -6alkyl)amino C_1 -6alkylcarbonyl, amino, C_1 -6alkylamino, C_1 -6alkylcarbonylamino, or a radical or formula -Alk-OR¹⁰ or -Alk-NR¹¹R¹²;

25 wherein Alk is C_1 -6alkanediyl;

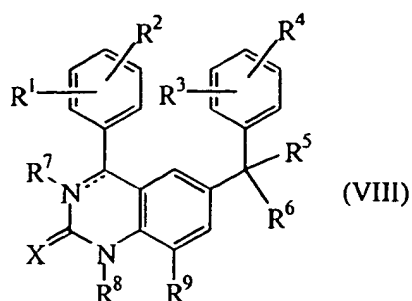
R^{10} is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, hydroxy C_1 -6alkyl, Ar^9 or Ar^9 - C_1 -6alkyl;

R^{11} is hydrogen, C_1 -6alkyl, C_1 -6alkylcarbonyl, Ar^{10} or

30 Ar^{10} - C_1 -6alkyl;

R^{12} is hydrogen, C_1 -6alkyl, Ar^{11} or Ar^{11} - C_1 -6alkyl; and

Ar^1 to Ar^{11} are each independently selected from phenyl; or phenyl substituted with halo, C_1 -6alkyl, C_1 -6alkyloxy or trifluoromethyl.



the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

the dotted line represents an optional bond;

5 X is oxygen or sulfur;

R¹ and R² each independently are hydrogen, hydroxy, halo, cyano, C₁-6alkyl, trihalomethyl, trihalomethoxy, C₂-6alkenyl, C₁-6alkyloxy, hydroxyC₁-6alkyloxy, C₁-6alkyloxyC₁-6alkyloxy, C₁-6alkyloxycarbonyl, aminoC₁-6alkyloxy, mono- or di(C₁-6alkyl)aminoC₁-6alkyloxy, Ar¹, Ar¹C₁-6alkyl, Ar¹oxy or Ar¹C₁-6alkyloxy;

R³ and R⁴ each independently are hydrogen, halo, cyano, C₁-6alkyl, C₁-6alkyloxy, Ar¹oxy, C₁-6alkylthio, di(C₁-6alkyl)amino, trihalomethyl or trihalomethoxy;

10 R⁵ is hydrogen, halo, C₁-6alkyl, cyano, haloC₁-6alkyl, hydroxyC₁-6alkyl, cyanoC₁-6alkyl, aminoC₁-6alkyl, C₁-6alkyloxyC₁-6alkyl, C₁-6alkylthioC₁-6alkyl, aminocarbonylC₁-6alkyl, C₁-6alkyloxycarbonylC₁-6alkyl, C₁-6alkylcarbonyl-C₁-6alkyl, C₁-6alkyloxycarbonyl, mono- or di(C₁-6alkyl)aminoC₁-6alkyl, Ar¹, Ar¹C₁-6alkyloxyC₁-6alkyl; or a radical of formula

20 -O-R¹⁰ (a-1),
-S-R¹⁰ (a-2),
-N-R¹¹R¹² (a-3),

wherein R¹⁰ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar¹, Ar¹C₁-6alkyl, C₁-6alkyloxycarbonylC₁-6alkyl, or a radical of formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵;

25 R¹¹ is hydrogen, C₁-6alkyl, Ar¹ or Ar¹C₁-6alkyl;

R¹² is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, C₁-6alkyloxycarbonyl, C₁-6alkylaminocarbonyl, Ar¹, Ar¹C₁-6alkyl, C₁-6alkylcarbonyl-C₁-6alkyl, Ar¹carbonyl, Ar¹C₁-6alkylcarbonyl, aminocarbonyl-carbonyl, C₁-6alkyloxyC₁-6alkylcarbonyl, hydroxy, C₁-6alkyloxy, aminocarbonyl, di(C₁-6alkyl)aminoC₁-6alkylcarbonyl, amino,

30

-34-

C₁-6alkylamino, C₁-6alkylcarbonylamino,
or a radical or formula -Alk-OR¹³ or -Alk-NR¹⁴R¹⁵;
wherein Alk is C₁-6alkanediyl;

R¹³ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, hydroxy-

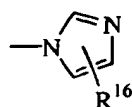
5

C₁-6alkyl, Ar¹ or Ar¹C₁-6alkyl;

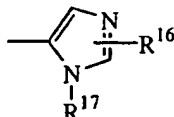
R¹⁴ is hydrogen, C₁-6alkyl, Ar¹ or Ar¹C₁-6alkyl;

R¹⁵ is hydrogen, C₁-6alkyl, C₁-6alkylcarbonyl, Ar¹ or
Ar¹C₁-6alkyl;

R⁶ is a radical of formula



(b-1),



(b-2),

10

wherein R¹⁶ is hydrogen, halo, Ar¹, C₁-6alkyl, hydroxyc₁-6alkyl, C₁-6alkyloxy-
C₁-6alkyl, C₁-6alkyloxy, C₁-6alkylthio, amino,
C₁-6alkyloxycarbonyl, C₁-6alkylthioC₁-6alkyl,
C₁-6alkylS(O)C₁-6alkyl or C₁-6alkylS(O)₂C₁-6alkyl;

15

R¹⁷ is hydrogen, C₁-6alkyl or di(C₁-4alkyl)aminosulfonyl;

R⁷ is hydrogen or C₁-6alkyl provided that the dotted line does not represent a bond;

R⁸ is hydrogen, C₁-6alkyl or Ar²CH₂ or Het¹CH₂;

R⁹ is hydrogen, C₁-6alkyl, C₁-6alkyloxy or halo; or

R⁸ and R⁹ taken together to form a bivalent radical of formula

20

-CH=CH- (c-1),

-CH₂-CH₂- (c-2),

-CH₂-CH₂-CH₂- (c-3),

-CH₂-O- (c-4), or

-CH₂-CH₂-O- (c-5);

25

Ar¹ is phenyl; or phenyl substituted with 1 or 2 substituents each independently
selected from halo, C₁-6alkyl, C₁-6alkyloxy or trifluoromethyl;

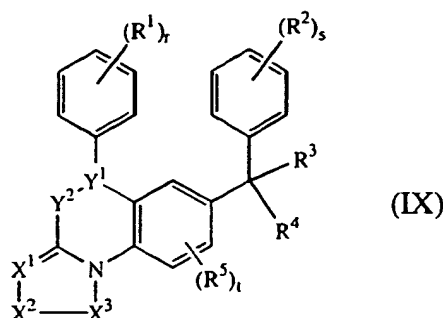
Ar² is phenyl; or phenyl substituted with 1 or 2 substituents each independently
selected from halo, C₁-6alkyl, C₁-6alkyloxy or trifluoromethyl; and

30

Het¹ is pyridinyl; pyridinyl substituted with 1 or 2 substituents each independently
selected from halo, C₁-6alkyl, C₁-6alkyloxy or trifluoromethyl

and

-35-



or the pharmaceutically acceptable acid addition salts and the stereochemically isomeric forms thereof, wherein

$=X^1-X^2-X^3-$ is a trivalent radical of formula

- 5 $=N-CR^6=CR^7-$ (x-1), $=CR^6-CR^7=CR^8-$ (x-6),
 $=N-N=CR^6-$ (x-2), $=CR^6-N=CR^7-$ (x-7),
 $=N-NH-C(=O)-$ (x-3), $=CR^6-NH-C(=O)-$ (x-8), or
 $=N-N=N-$ (x-4), $=CR^6-N=N-$ (x-9);
 $=N-CR^6=N-$ (x-5),

- 10 wherein each R^6 , R^7 and R^8 are independently hydrogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkyloxy, aryloxy, C_{1-4} alkyloxycarbonyl, hydroxy C_{1-4} alkyl, C_{1-4} alkyloxy- C_{1-4} alkyl, mono- or di(C_{1-4} alkyl)amino C_{1-4} alkyl, cyano, amino, thio, C_{1-4} alkylthio, arylthio or aryl;

$>Y^1-Y^2-$ is a trivalent radical of formula

- 15 $>CH-CHR^9-$ (y-1),
 $>C=N-$ (y-2),
 $>CH-NR^9-$ (y-3), or
 $>C=CR^9-$ (y-4);

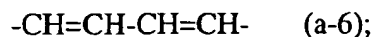
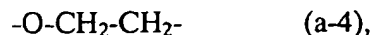
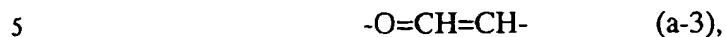
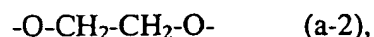
- 20 wherein each R^9 independently is hydrogen, halo, halocarbonyl, aminocarbonyl, hydroxy C_{1-4} alkyl, cyano, carboxyl, C_{1-4} alkyl, C_{1-4} alkyloxy, C_{1-4} alkyloxy C_{1-4} alkyl, C_{1-4} alkyloxycarbonyl, mono- or di(C_{1-4} alkyl)amino, mono- or di(C_{1-4} alkyl)-amino C_{1-4} alkyl, aryl;

r and s are each independently 0, 1, 2, 3, 4 or 5;

t is 0, 1, 2 or 3;

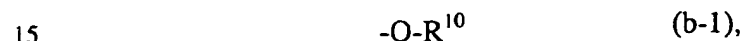
- 25 each R^1 and R^2 are independently hydroxy, halo, cyano, C_{1-6} alkyl, trihalomethyl, trihalomethoxy, C_{2-6} alkenyl, C_{1-6} alkyloxy, hydroxy C_{1-6} alkyloxy, C_{1-6} alkylthio, C_{1-6} alkyloxy C_{1-6} alkyloxy, C_{1-6} alkyloxycarbonyl, amino C_{1-6} alkyloxy, mono- or di(C_{1-6} alkyl)amino, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyloxy, aryl, aryl C_{1-6} alkyl, aryloxy or aryl C_{1-6} alkyloxy, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, amino-
 30 carbonyl, amino C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)aminocarbonyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl; or

two R^1 or R^2 substituents adjacent to one another on the phenyl ring may independently form together a bivalent radical of formula



R^3 is hydrogen, halo, C_{1-6} alkyl, cyano, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, cyano C_{1-6} alkyl, amino C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkylthio C_{1-6} alkyl, aminocarbonyl C_{1-6} alkyl, hydroxycarbonyl, hydroxycarbonyl C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, C_{1-6} alkylcarbonyl C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl, aryl, aryl C_{1-6} alkyloxy C_{1-6} alkyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl;

or a radical of formula



wherein R^{10} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, aryl, aryl C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, or a radical of formula $-\text{Alk}-\text{OR}^{13}$ or $-\text{Alk}-\text{NR}^{14}\text{R}^{15}$;

R^{11} is hydrogen, C_{1-6} alkyl, aryl or aryl C_{1-6} alkyl;

R^{12} is hydrogen, C_{1-6} alkyl, aryl, hydroxy, amino, C_{1-6} alkyloxy, C_{1-6} alkylcarbonyl C_{1-6} alkyl, aryl C_{1-6} alkyl, C_{1-6} alkylcarbonylamino, mono- or di(C_{1-6} alkyl)amino, C_{1-6} alkylcarbonyl, aminocarbonyl, arylcarbonyl, halo C_{1-6} alkylcarbonyl, aryl C_{1-6} alkylcarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkyloxy C_{1-6} alkylcarbonyl, mono- or di(C_{1-6} alkyl)aminocarbonyl wherein the alkyl moiety may optionally be substituted by one or more substituents independently selected from aryl or C_{1-3} alkyloxycarbonyl, aminocarbonylcarbonyl, mono- or di(C_{1-6} alkyl)amino C_{1-6} alkylcarbonyl, or a radical or formula $-\text{Alk}-\text{OR}^{13}$ or $-\text{Alk}-\text{NR}^{14}\text{R}^{15}$;

wherein Alk is C_{1-6} alkanediyl;

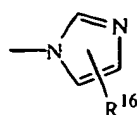
R^{13} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, hydroxy C_{1-6} alkyl, aryl or aryl C_{1-6} alkyl;

R^{14} is hydrogen, C_{1-6} alkyl, aryl or aryl C_{1-6} alkyl;

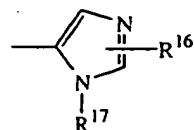
R^{15} is hydrogen, C_{1-6} alkyl, C_{1-6} alkylcarbonyl, aryl or aryl C_{1-6} alkyl;

R^4 is a radical of formula

-37-



(c-1),



(c-2),

wherein R^{16} is hydrogen, halo, aryl, C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkylthio, amino, mono- or di(C_{1-4} alkyl)amino, hydroxycarbonyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylthio C_{1-6} alkyl,

5 C_{1-6} alkylS(O) C_{1-6} alkyl or C_{1-6} alkylS(O) $_2$ C_{1-6} alkyl;

R^{16} may also be bound to one of the nitrogen atoms in the imidazole ring of formula (c-1) or (c-2), in which case the meaning of R^{16} when bound to the nitrogen is limited to hydrogen, aryl, C_{1-6} alkyl, hydroxy C_{1-6} alkyl,

10 C_{1-6} alkyloxy C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl, C_{1-6} alkylS(O) C_{1-6} alkyl or C_{1-6} alkylS(O) $_2$ C_{1-6} alkyl;

R^{17} is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, aryl C_{1-6} alkyl, trifluoromethyl or di(C_{1-4} alkyl)aminosulfonyl;

R^5 is C_{1-6} alkyl, C_{1-6} alkyloxy or halo;

aryl is phenyl, naphthalenyl or phenyl substituted with 1 or more substituents each

15 independently selected from halo, C_{1-6} alkyl, C_{1-6} alkyloxy or trifluoromethyl.

2. A combination as claimed in claim 1 wherein the farnesyl protein transferase inhibitor is a compound of formula (I) wherein X is oxygen and the dotted line represents a bond.

20

3. A combination as claimed in claim 1 or claim 2 wherein the farnesyl protein transferase inhibitor is a compound of formula (I) wherein R^1 is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl or mono- or di(C_{1-6} alkyl)amino C_{1-6} alkyl and wherein R^3 is hydrogen and R^2 is halo, C_{1-6} alkyl, C_{2-6} alkenyl, C_{1-6} alkyloxy, trihalomethoxy or hydroxy C_{1-6} alkyloxy.

25

4. A combination as claimed in any of the preceding claims wherein the farnesyl protein transferase inhibitor is a compound of formula (I) wherein R^8 is hydrogen, hydroxy, halo C_{1-6} alkyl, hydroxy C_{1-6} alkyl, cyano C_{1-6} alkyl, C_{1-6} alkyloxycarbonyl C_{1-6} alkyl, imidazolyl, or a radical of formula $-NR^{11}R^{12}$ wherein R^{11} is hydrogen or C_{1-12} alkyl and R^{12} is hydrogen, C_{1-6} alkyl, C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkylcarbonyl, hydroxy, or a radical of formula $-Alk^2-OR^{13}$ wherein R^{13} is hydrogen or C_{1-6} alkyl.

30

5. A combination as claimed in claim 1 wherein the farnesyl transferase inhibitor is selected from:
 4-(3-chlorophenyl)-6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)-methyl]-1-methyl-2(1*H*)-quinolinone,
 5 6-[amino(4-chlorophenyl)-1-methyl-1*H*-imidazol-5-ylmethyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone;
 6-[(4-chlorophenyl)hydroxy(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone;
 6-[(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone monohydrochloride monohydrate;
 10 6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-ethoxyphenyl)-1-methyl-2(1*H*)-quinolinone, and
 6-amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-1-methyl-4-(3-propylphenyl)-2(1*H*)-quinolinone; a stereoisomeric form thereof or a
 15 pharmaceutically acceptable acid or base addition salts thereof.
6. A combination as claimed in claim 1 wherein the farnesyl transferase inhibitor is (+)-6-[amino(4-chlorophenyl)(1-methyl-1*H*-imidazol-5-yl)methyl]-4-(3-chlorophenyl)-1-methyl-2(1*H*)-quinolinone; or a pharmaceutically acceptable acid
 20 addition salt thereof.
7. A combination as claimed in claim 1 wherein the farnesyl protein transferase inhibitor is a compound of formula (IX) wherein $=X^1-X^2-X^3$ is a trivalent radical of formula (x-2), (x-3) or (x-4), $>Y^1-Y^2$ is a trivalent radical of formula (y-2), (y-3) or (y-4), r and s are 1, t is 0, R^1 is halo, preferably chloro, and most preferably 3-chloro or R^1 is C_{1-4} alkyl, preferably 3-methyl, R^2 is halo, preferably chloro, and most preferably 4-chloro, R^3 is a radical of formula (b-1) or (b-3), R^4 is a radical of formula (c-2), R^6 is C_{1-4} alkyl, R^9 is hydrogen, R^{10} and R^{11} are hydrogen and R^{12} is hydrogen or hydroxy.
 25
 30
8. A combination as claimed in claim 1 wherein the farnesyl protein transferase inhibitor is 5-(3-chlorophenyl)- α -(4-chlorophenyl)- α -(1-methyl-1*H*-imidazol-5-yl)tetrazolo[1,5-a]quinazoline-7-methanamine or a pharmaceutically acceptable acid addition salt thereof.
 35
9. A combination as claimed in any of the preceding claims in the form of a pharmaceutical composition comprising trastuzumab and a farnesyl transferase inhibitor selected from compounds of formulae (I), (II), (III), (IV), (V), (VI), (VII),

(VIII) and (IX) (as defined in claim 1) together with one or more pharmaceutical carriers.

10. A combination as claimed in any of the preceding claims for use in medical therapy.

5

11. A combination as claimed in claim 11 for inhibiting the growth of tumor cells.

12. Use of a combination as claimed in any of claims 1 to 11 in the manufacture of a pharmaceutical composition for inhibiting the growth of tumor cells.

10

13. A method of inhibiting the growth of tumor cells in a human subject which comprises administering to the subject an effective amount of a combination as claimed in any of claims 1 to 11.

15